Risk factors for contact lens-related microbial keratitis in Singapore

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CLINICAL STUDY

Abstract

Purpose: To investigate independent risk factors for contact lens-related microbial keratitis in Singapore and estimate their impact on disease load.

Methods: Cases were contact lens wearers presenting to Singapore National Eye Centre with microbial keratitis between 2008 and 2010. Community contact lens wearers were recruited as controls. All wearers completed a previously validated questionnaire describing contact lens wear history, hygiene and compliance habits, and demographics. Risk factors significant in univariate analysis ($P < 0.2$) were evaluated in a multivariate model.

Results: In all, 58 cases of microbial keratitis and 152 contemporaneous controls were identified. When controlling for other variables, Chinese had a $7 \times$ lower risk compared with other races (95% CI: 2.3–21.3, $P = 0.001$). Those aged between 25 and 44 years were at $3 \times$ increased risk compared with younger wearers (95% CI: 1.1–9.6, $P = 0.04$). Occasional overnight contact lens wear (less often than one night per week) was associated with a $4 \times$ higher risk (95% CI: 1.2–15.4, $P = 0.03$) compared with daily use. Not washing hands before handling was associated with a $13 \times$ increased risk (95% CI: 1.9–84.8, $P = 0.008$). Use of multipurpose solution A carried a $16 \times$ higher risk compared with hydrogen peroxide (95% CI: 1.5–174.0, $P = 0.02$). The combined PAR% for modifiable risk factors (occasional overnight wear, not washing of hands, and MPS A) was 82%.

Conclusions: Consistent with previous findings, independent risk factors for contact lens-related microbial keratitis include poor hand hygiene, occasional overnight wear, and type of lens care solution. Prolonged overnight or extended contact lens use was infrequent in this population.

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Introduction

Contact lenses are a common means of reversible vision correction that offer cosmetic and optical advantages over spectacles. There are an estimated 140 million individuals who wear contact lenses worldwide.¹

Complications of contact lens wear are generally self-limiting on lens removal with the exception of contact lens-related microbial keratitis, a rare but potentially sight-threatening condition. Epidemiological studies of contemporary contact lenses have estimated the incidence of microbial keratitis in daily wear at 3 to 5 per 10 000 lens wearers per year, with incidence varying according to wear modality.^{2–6}

Risk factors that have been consistently identified may be categorised into either modifiable or nonmodifiable risk factors. Modifiable risk factors include extended and overnight contact lens wear,^{7,8} poor hand hygiene,^{4,9} infrequent or omission of lens disinfection,^{7,8} case hygiene and case replacement,^{6,10} and smoking.^{4,6,11} Nonmodifiable risk factors include gender,^{2,7,11} young age,^{2,7} and socioeconomic status.⁹ Systemic risk factors for contact lens-related microbial keratitis include poor general health,¹² diabetes,⁹ and thyroid disease.¹² More recently, lens supply has been implicated as a risk factor where internet or mail order supply of contact lenses has been associated with a higher risk of microbial keratitis compared with obtaining lenses through a contact lens practitioner.^{6,13}

Factors identified as contributing to the severity of microbial keratitis include pathogenic or environmental microorganisms^{14,15} and high daytime temperatures, such as in tropical regions like Singapore.¹⁵

Patterns of contact lens prescribing, lens supply, wearer behaviour, and environmental microbiota vary across different cultures and climates. These may affect the risk of contact lens-related microbial keratitis. It is therefore

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important to examine specific populations to determine specific risk factors associated with the use of contact lenses in these populations. This study reports risk factors for contact lens-related microbial keratitis in Singapore and estimates the impact of these risk factors on disease load.

Materials and methods

Case ascertainment

New cases of contact lenses-related microbial keratitis were identified in a 32-month prospective study of wearers presenting to the Singapore National Eye Centre (SNEC), a tertiary ophthalmic referral centre, between January 2008 and August 2010.

The definition of microbial keratitis was chosen to align with previous reports of contact lens-related microbial keratitis.^{6,13,16} In brief, microbial keratitis was defined by either a positive corneal culture or a corneal infiltrate and overlying epithelial defect with ONE OR MORE of the following characteristics:

- Any part of the lesion within or overlapping the central 4 mm of the cornea
- Uveitis
- Pain

Written consent was obtained from cases to allow access to medical records and subjects completed a self-administered questionnaire^{6,13,16,17} to establish potential risk factors, including contact lens type, wear habits, hygiene compliance and history, and demographics. Risk factors considered in the analysis are shown in Table 1. Human research ethics approval was obtained from the

University of New South Wales Human Research Ethics Committee and from Singapore National Eye Centre, and the study was conducted in accordance with the tenets of the Declaration of Helsinki. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this study.

Identification of controls and eligibility

Contact lens-wearing community controls without microbial keratitis were identified from either contact lens practitioners or recruited from community venues. Three nonmatched controls were identified per case. Controls completed an identical questionnaire that was either self-administered or completed during a face-to-face interview with interviewers not associated with their eye care.

Eligible contact lens wearers were individuals aged 14–67 years who had worn their lenses in the 4 weeks before the event (cases) or before the survey (controls) for the correction of low refractive errors. Patients with keratoconus, aphakia, or those wearing bandage contact lenses were excluded from this study.

Study definitions

Study definitions specific to this study are described below. Other definitions are common to previously published studies and have been described elsewhere.¹³

Positive culture

Corneal specimens were cultured in both aerobic and anaerobic conditions utilising a variety of culture media. A positive bacterial culture was defined as successful isolation of any organism from a specimen in two or more different culture media.

Overnight wear

Contact lens wearers reporting overnight wear were categorised into one of two groups; either occasional overnight contact lens wearers (reporting overnight wear of less than one night per week) or regular overnight contact lens wearers (one or more nights per week). Participants who did not report any overnight wear were categorised as 'strict daily-wear users'.

Socioeconomic status

Socioeconomic status (SES) was included as a potential risk factor. The International Standard Classification of Occupations (ISCO-88) was considered as a surrogate measure of SES. Study participants were categorised into higher-skilled (ISCO 1–3) and lower-skilled occupations

Table 1 Risk factors

Demographic information	Gender
	Race
	Age
	Occupation
	Education
Lens wear history	Duration of contact lens wear
	Lens replacement frequency
	Wear schedule
	Overnight wear
Lens details	Type of lens used
	Lens care solution used
	Regular lens case replacement
	Lens case hygiene
Water exposure	Showering while wearing lenses
	Time of day shower taken
	Swimming while wearing lenses
Hand hygiene	Washing and/or drying hands before handling lenses
Other behavioural factors	Travel history over the past 3 months

(ISCO 4–9). In participants who were either schooling or conscripted into compulsory national service, their parents' highest rated occupation was used as in lieu of their occupations.

Education levels were also considered a potential surrogate measure for SES. Participants were categorised according to their years of education and highest academic qualifications received. Those indicating upper-secondary or lower as the highest level of education achieved were grouped together, whereas those with diplomas, professional, or tertiary-level qualifications were placed in another category. Participants who did not fall into either category were classified as 'others'.

Hand hygiene

Hand hygiene habits before handling of contact lenses were examined. Participants were placed in one of three categories: those who washed and dried their hands, only washed their hands without drying, and participants that neither washed nor dried their hands before handling their contact lenses.

Statistical analysis

Microbial keratitis was the outcome of interest in this study. Potential risk factors identified were tested for statistical significance with univariate analysis using the χ^2 test of independence for proportions. Variables with a $P < 0.2$ on univariate analysis were further evaluated in a multivariate model. In this model, point estimates of odds ratios were derived utilising binomial logistic regression analysis. These results were subsequently used to determine the degree of association between factors.

Risk factors considered in the construction of the final multivariate model have been listed in Table 1. Variables retained in the multivariate model were factors that either led to an improvement in the χ^2 value or identified as confounding factors. Interactions between variables were also examined and included in the model if statistically significant ($P < 0.05$). The strength of association between significant factors is represented by the odds ratios and confidence intervals. All statistical analyses were performed using SPSS software (version 21.0, SPSS Inc., Chicago, IL, USA).

Other statistical tests used in our analysis include the Hosmer–Lemeshow test and variance inflation factor (VIF) analysis. Nagelkerke R^2 value was also calculated. Furthermore, univariate and combined population attributable risk percentage (PAR%) were also calculated to evaluate the disease load associated with each risk factor. These permit an estimation of the number of cases that could be eliminated if a particular risk factor was removed.

Results

A total of 58 cases of microbial keratitis and 152 controls were identified. All participants were included in the final analysis. Demographic data and information on lens types and wear schedule for this cohort of patients have been summarised in Tables 2 and 3.

Univariate analysis

The racial composition of our study cohort was compared against Singaporean population census data in 2010 from the Singapore Department of Statistics.¹⁸ Chinese were underrepresented whereas Malays were overrepresented within the cases when compared with both controls and census data. The differences in racial distribution between cases and controls were statistically significant ($P = 0.008$).

Individuals between the ages of 14 and 24 years were also overrepresented among controls. Correspondingly, there appeared to be a greater proportion of 25–44-year-old individuals among cases compared with controls ($P < 0.001$).

In analysing the educational qualifications of our cohort, a larger proportion of cases were found to have a diploma, university, masters or doctorate degree, or other professional qualifications compared with controls ($P = 0.100$).

In terms of lens wear history, the majority of cases had worn contact lenses for ≥ 5 years compared with controls ($P < 0.001$). In comparison with controls, a significant proportion of cases comprised frequent contact lens users, using their lenses for > 4 days each week ($P < 0.001$). A larger percentage of controls wore contact lenses for less than a day each week compared with cases. Cases were more likely to wear lenses overnight for ≥ 2 nights ($P = 0.020$).

A greater proportion of cases, compared with controls, used planned replacement lenses, defined as weekly, fortnightly, and monthly replacements. Monthly replacement was the most common modality ($P < 0.001$). Correspondingly, there was a smaller proportion of daily disposable lens wearers among cases compared with controls ($P = 0.006$).

Lenses were also categorised and analysed based on their attributes. A larger proportion of cases compared with controls wore silicone hydrogel lenses and cosmetic (lenses to change eye colour) lenses, although this consisted of a small proportion of the total study cohort ($P = 0.001$).

Other significant risk factors identified, when comparing cases with controls, include certain multipurpose solution types ($P < 0.001$), water exposure resulting from activities such as showering while wearing lenses ($P = 0.008$), and poor hand hygiene ($P = 0.002$).

Table 2 Demographic risk factors

Risk factors	Cases and control groups (%)		2010 Census Data, '000 (%)	P-value
	Microbial keratitis, n = 58	Controls, n = 152		
<i>Gender</i>				0.481
Male	26 (44.8)	60 (39.5)	1861.1 (49.3)	
Female	32 (55.2)	92 (60.5)	1910.6 (50.7)	
<i>Race</i>				0.008
Chinese	37 (63.8)	129 (84.9)	2794 (74.1)	
Malay	12 (20.7)	13 (8.6)	503.9 (13.4)	
Indian	6 (10.3)	5 (3.3)	348.1 (9.7)	
Others	3 (5.2)	5 (3.3)	125.8 (3.3)	
<i>Age</i>				<0.001
14–24	24 (41.4)	101 (66.9)	30.9%	
25–44	33 (56.96)	35 (23.2)	31.8%	
45–67	1 (1.7)	15 (9.9)	37.3%	
<i>ISCO classification</i>				0.977
ISCO 1–3	36 (73.5)	98 (73.7)		
ISCO 4–9	13 (26.5)	35 (26.3)		
<i>Education</i>				0.100
Lower primary to upper secondary	17 (29.3)	33 (21.7)		
Diplomas, university degrees, and other professional qualifications	38 (65.5)	84 (55.3)		
Others	3 (5.2)	35 (23.0)		

Abbreviation: ISCO, International Standard Classification of Occupation.

Microbiology results

Corneal specimens were obtained for microbiological analysis when possible. Data were available for 46 cases. Of these, missing data were reported for 16 patients and they were excluded from the final analysis. A summary of the microbiology results is shown in Table 4.

Out of the remaining 30 cases, 14 positive corneal culture results (46.7%) were identified (Table 4). In all, 12 cultures were positive for *Pseudomonas aeruginosa*, 1 culture positive for *Serratia* sp., and 1 culture positive for coagulase-negative *Staphylococcus*.

Multivariate analysis

Independent risk factors are shown in Table 5. After adjusting for risk factors identified on univariate analysis, Chinese were found to be at a 7 times lower risk of developing microbial keratitis compared with other races. Those aged between 25 and 44 years were 3 times more likely to develop microbial keratitis compared with younger wearers. Not washing hands before lens handling was associated with a 13-fold increase in risk, whereas occasional overnight wear was found to increase the risk of developing microbial keratitis by fourfold. Patients with microbial keratitis were also more likely to use multipurpose solution A (a sterile, isotonic, buffered

solution, preserved with polyhexamethylene biguanide (0.0001%), a phosphate buffer, poloxamer 237, edetate disodium, sodium chloride, potassium chloride, and purified water) when compared with hydrogen peroxide.

The Hosmer–Lemeshow test for logistic regression was performed, demonstrating the goodness of fit of the multivariate model ($P = 0.506$). The Nagelkerke R^2 value indicated that this multivariate model accounted for ~49.0% of the variance. VIF analysis was also performed and multicollinearity was not detected, with the VIF not exceeding 3 in any of our analyses.

The univariate PAR% for all independent, modifiable risk factors is shown in Table 5. The combined PAR% for occasional overnight wear, not washing of hands, and use of MPS A is 81.8%.

Discussion

This is the first study to measure the risks of all contact lens-related microbial keratitis in Singapore. Microbial keratitis is a disease associated with significant morbidity and identification of modifiable risk factors is important in the ongoing management and prevention of this disease. A cross-sectional survey performed by Lee *et al*¹⁹ has suggested that ~9% of the Singaporean population are contact lens wearers. Extrapolating from 2010

Table 3 Contact lens-related factors associated with microbial keratitis

	Microbial keratitis and control groups (%)		P-value
	Microbial keratitis, n = 58	Controls, n = 152	
<i>Duration of lens wear</i>			<0.001
1–6 Months	3 (5.2)	21 (13.9)	
7 Months to 5 years	18 (31.0)	79 (52.3)	
≥ 6 Years	37 (63.8)	51 (33.8)	
<i>Wear schedule</i>			0.005
<1 Day	1 (1.7)	30 (19.9)	
1–4 Days	14 (24.1)	41 (27.2)	
>4 Days	43 (74.1)	80 (53.0)	
<i>Overnight wear</i>			0.020
Strict DW	43 (74.1)	136 (89.5)	
Occasional ON	14 (24.1)	15 (9.9)	
Regular ON	1 (1.7)	1 (0.7)	
<i>Lens replacement</i>			<0.001
Daily	6 (10.3)	43 (28.3)	
Weekly, fortnightly, or monthly	51 (87.9)	89 (58.6)	
Yearly	1 (1.7)	20 (13.2)	
<i>Lens types</i>			0.001
Daily disposable soft lenses	11 (20.0)	43 (28.3)	
Silicone hydrogel	14 (25.5)	25 (16.4)	
Non-silicone hydrogel	25 (45.5)	64 (42.1)	
Cosmetic	4 (7.3)	0 (0)	
Conventional	0 (0)	16 (10.5)	
Rigid lenses	1 (1.8)	4 (2.6)	
<i>Lens care solutions</i>			<0.001
Hydrogen peroxide solutions	1 (1.9)	9 (8.0)	
MPS A	26 (50.0)	16 (14.3)	
Other MPS	25 (48.1)	87 (77.7)	
<i>Water exposure</i>			0.008
Showering			
Not showering with lenses	29 (50)	106 (70.7)	
Showering with lenses	28 (48.3)	44 (29.3)	
<i>Hand hygiene</i>			0.002
Washing/drying hands before handling CL			
Wash and dry	23 (39.7)	94 (61.8)	
Wash only	28 (48.3)	54 (35.5)	
Neither wash nor dry	7 (12.1)	4 (2.6)	
<i>Hygiene score</i>			0.268
Poor	13 (24.1)	17 (14.9)	
Moderate	16 (29.6)	30 (26.3)	
Good	7 (13.0)	12 (10.5)	
Excellent	18 (33.3)	55 (48.2)	

Abbreviations: DW, daily wear; MPS, multipurpose solution; ON, overnight.

population census data,¹⁸ this translates to ~456 903 contact lens wearers during the study period and this would result in ~200 wearers developing microbial keratitis each year in Singapore.⁶ Given access to primary eye care in Singapore, these acute cases would be

managed through tertiary care centres and this approach is likely to capture a representative sample of cases.

Given the unique sociocultural, environmental, and climate conditions, along with differences in contact lens prescribing practice and eye care availability, it is

conceivable that risk factors of contact lens wearers in Singapore may differ from those previously reported.

Age and race were important sociodemographic factors. Chinese were found to be at a lower risk of developing microbial keratitis compared with other races. This is consistent with findings in a Singaporean fungal keratitis case-control study that found that Chinese wearers were at a lower risk of developing *Fusarium* keratitis.²⁰ A multicentre cross-sectional survey of contact lens complications in Singapore found that 77% of patients who presented with complications were Chinese.²¹ However, no disease-free lens wearing controls were included in the published study.

Table 4 Positive corneal cultures

Microbial organism cultured	Number of positive cultures (%)
<i>Pseudomonas aeruginosa</i>	12 (85.7)
<i>Serratia</i> sp.	1 (7.1)
Coagulase-negative <i>Staphylococcus</i>	1 (7.1)
Total	14

The differences in risk profile among racial subgroups may be attributed to disparities in health-related quality of life. Clinically significant differences have been demonstrated among various racial groups in Singapore,²² where Chinese scored highest in five out of eight scales of the Short Form Health Survey (SF-36) compared with their Malay and Indian counterparts. This instrument is a validated, self-administered questionnaire that measured health-related quality of life across various domains, with higher scores indicative of better-perceived health.

Although socioeconomic class was not identified as an independent risk factor, race may be considered a surrogate measure, as the most recent population census demonstrated significant differences in average monthly household incomes between different racial groups.²³ Both Chinese and Indian households demonstrated similar earning power that was higher than the average monthly Malay household income. This is consistent with study findings reporting an association between low socioeconomic class and increased risk of keratitis.⁹ However, findings in other studies shown higher socioeconomic class to be linked to an increased risk of

Table 5 Independent risk factors for microbial keratitis

Risk factor	Odds ratio (OR)	95% CI	P-value	PAR%
<i>Race</i>				
Chinese	1.00 (Referent)			
Other races	7.02	2.32–21.29	0.001	83.6%
<i>Age (years)</i>				
14–24	1.00 (Referent)			
25–44	3.2	1.07–9.57	0.037	33.8%
45–67	0.25	0.02–2.73	0.255 ^a	
<i>Duration</i>				
1–6 Months	1.00 (Referent)			
7 Months to 5 years	0.43	0.08–2.29	0.320 ^a	NA
≥ 6 Years	1.7	0.31–9.52	0.544 ^a	
<i>Overnight wear</i>				
Strict daily wear	1.00 (Referent)			
Occasional overnight wear	4.26	1.18–15.37	0.027	24.3%
Overnight wear	1.89	0.09–40.80	0.684 ^a	
<i>Washing and drying of hands</i>				
Wash and dry	1.00 (Referent)			
Wash only	1.92	0.70–5.28	0.207 ^a	
Not washing	12.77	1.93–84.78	0.008	23.7%
<i>Multipurpose solutions</i>				
Hydrogen peroxide solutions	1.00 (Referent)			
MPS A	16.2	1.52–174.03	0.021	68.5%
Other MPS	2.3	0.23–22.02	0.482 ^a	

Abbreviations: CI, confidence interval; MPS, multipurpose solution.

Individual univariate population attributable risk percentages (PAR%) may add up to >100% because exposures are not mutually exclusive.

^aNot significantly different.

microbial keratitis.^{6,8,16} Further research is required to establish the association between race, SES, and microbial keratitis and any potential confounders.

Those aged between 25 and 44 years had an increased risk of developing microbial keratitis compared with younger wearers aged between 14 and 24 years. Previous studies have described a higher risk in younger age groups,^{3,13} and this finding is unexpected.

Certain contact lens wear practices have also been associated with an increased risk of developing contact lens-related microbial keratitis. Occasional overnight wear was independently associated with an increased risk of developing contact lens-related microbial keratitis. This was consistent with previous studies of contact lens-related microbial keratitis.^{6,13} However, regular overnight lens wear was not identified as a significant risk factor in our multivariate model, likely reflecting the limited penetrance of extended wear in Singapore. This finding was consistent with 2012 fitting data from Singapore demonstrating limited uptake of extended wear soft contact lenses (personal communication, Morgan and Woods, 2012).

Not washing of hands before handling contact lenses was identified as a risk factor on multivariate analysis, accounting for 24% of the disease load. Poor hand hygiene has been consistently previously reported as a risk factor.^{6,13,16} Poor hand hygiene may result in the introduction of possible pathogens during lens insertion and lens manipulation during wear and microbial contamination of storage cases.²⁴ This is an important compliance message both for the initial dispensing of contact lenses and during aftercare visits.

The use of MPS A was associated with an increased risk of developing contact lens-related microbial keratitis, accounting for 69% of the disease load. This represents a very high risk to contact lens users and was independent of other hygiene and compliance factors. Similar findings have been described in a separate study examining risk factors in an Australian population with moderate and severe contact lens-related microbial keratitis in daily wear lens users.¹⁶ Previously published studies have also reported associations between certain multipurpose solution types and *Fusarium* and *Acanthamoeba* outbreaks of contact lens-related microbial keratitis.^{25–27}

Certain polymeric biguanide-based care solutions have been demonstrated to be less effective against bacterial biofilms in comparison with hydrogen peroxide or polyquaternium-based solutions.²⁸ In addition, reduction in microbial efficacy of this product has been reported when used for the storage of contact lenses in lens cases over a prolonged period of time.²⁹ The increased risk identified with the use of MPS A in both clinical and laboratory studies may suggest failure to achieve a

suitable level of disinfection efficacy particularly in the hands of the wearer.

Other compliance factors, such as case hygiene practice and disinfection frequency, were not identified as significant factors in this study, and this was unexpected given the strong association with microbial keratitis in daily wear use.

Microbiological findings in this study are similar to those reported by Dart *et al*,¹³ and are broadly consistent with existing literature reports of *P. aeruginosa* as the most prevalent organism isolated in 50–60% of culture-proven contact lens-related disease.^{16,30–33} Environmental organisms were recovered in all but one of the culture-positive corneal samples and, although these numbers are low, this finding would be consistent with higher recovery of environmental causative organisms in tropical climate zones.¹⁵ *P. aeruginosa* is a common environmental pathogen that is able to survive in contact lens storage cases.^{34,35} It demonstrates a greater ability to adhere to contact lenses compared with other bacteria,³⁶ and is associated with both a more severe disease spectrum and poorer visual prognosis.¹⁴ Our study findings therefore highlight the importance of prompt identification and management of microbial keratitis to limit disease severity and optimise patient outcomes.

Limitations to this study have been recognised. The multivariate model accounts for approximately half of the variance in the data. This suggests that other health-related or behavioural risk factors not surveyed in this study are likely to be important.

In addition, the selection of controls to minimise selection bias in case-control studies is challenging. Potential sampling biases from techniques employed in recruiting controls may have been encountered in this study. Differences between the composition of our control group and 2010 census data were also identified. Chinese were overrepresented, whereas Malays and Indians were underrepresented in our control population. However, there is limited information on the contact lens-related population characteristics in Singapore. Furthermore, the control group in this study is consistent with the typical profile of contact lens wearers elsewhere.³⁷

In conclusion, our findings have implications for the prevention and management of microbial keratitis in Singapore. Contact lens-related microbial keratitis was associated with race, wearer age, occasional overnight wear, poor hand hygiene, and lens care solution type. The high PAR% for infection associated with a particular solution product available in Singapore is of significant concern. Modifiable risk factors may be amenable to education of contact lens wearers by eye care providers. Previous studies have indicated more severe disease because of environmental organisms occurring more commonly in frequent replacement daily wear users

compared with daily disposable users. Given the high rate of environmental organisms recovered, daily disposable contact lenses may be a safer alternative to reduce morbidity.^{6,38}

Summary

What was known before

- Independent risk factors for contact lens-related microbial keratitis, including poor hand hygiene, occasional overnight wear, and type of lens care solution, have been identified in previous studies.

What this study adds

- This is the first study to measure risks of contact lens-related microbial keratitis in Singapore. Differences in risk profiles between ethnicities were identified in our multivariate model.

Conflict of interest

The authors declare no conflict of interest.

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